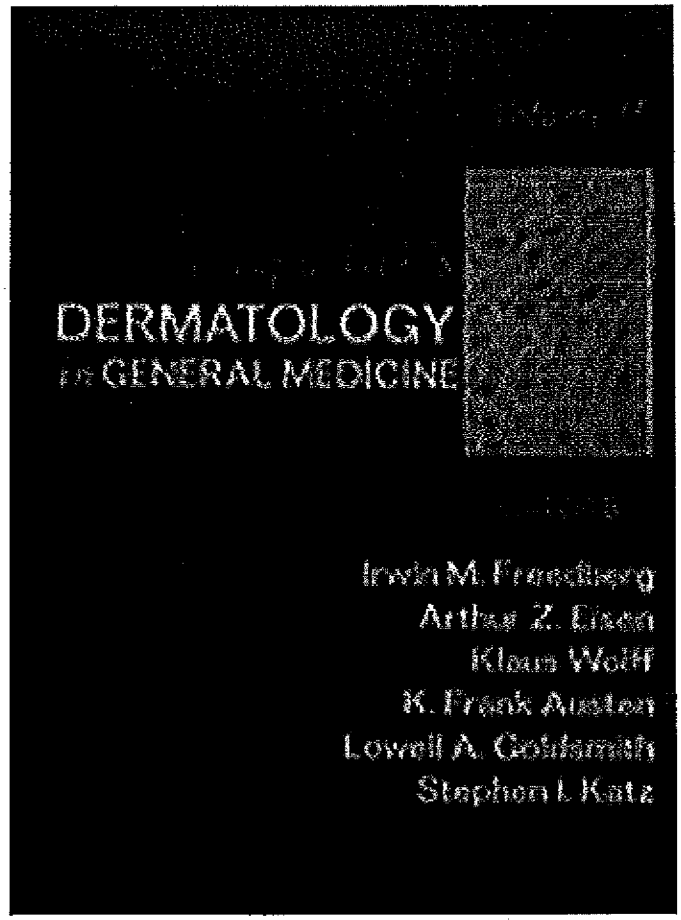
Exhibit B


DERMATOLOGY
in GENERAL MEDICINE
Irwin M. Freedberg
Arthur Z. Eisen
Klaus Wolff
K. Frank Austen
Lowell A. Goldsmith
Stephen I. Katz

113. Kurwa HA et al: A randomized paired comparison of photodynamic therapy and topical 5-fluorouracil in the treatment of actinic keratoses. *J Am Acad Dermatol* 41:414, 1999
114. Morton CA et al: Comparison of photodynamic therapy with cryotherapy in the treatment of Bowen's disease. *Br J Dermatol* 135:766, 1996
115. Haller JC et al: Routine double treatments of superficial basal cell carcinomas using aminolaevulinic acid-based photodynamic therapy. *Br J Dermatol* 143:1270, 2000
116. Wang I et al: Photodynamic therapy vs. cryosurgery of basal cell carcinomas: results of a phase III clinical trial. *Br J Dermatol* 144:832, 2001
117. Wolf P et al: Topical photodynamic therapy with endogenous porphyrins after application of 5-aminolevulinic acid. *J Am Acad Dermatol* 28:17, 1993
118. Calzavara-Pinton PG: Repetitive photodynamic therapy with topical delta-aminolevulinic acid as an appropriate approach to the routine treatment of superficial non-melanoma skin tumours. *J Photochem Photobiol B Biol* 29:53, 1995
119. Weinstein GD et al: Photodynamic therapy (PDT) of psoriasis with topical delta aminolevulinic acid (ALA): A pilot dose ranging study. *Photodermatol Photoimmunol Photomed* 10:93, 1994
120. Karrer S et al: Topical photodynamic therapy for localized scleroderma. *Acta Dermatol Venereol* 80:26, 2000
121. Frank RGJ et al: Photodynamic therapy for condylomata acuminata with local application of 5-aminolevulinic acid. *Genitourin Med* 72:70, 1996
122. Karrer S et al: Epidermodysplasia verruciformis treated using topical 5-aminolevulinic acid photodynamic therapy. *Br J Dermatol* 140:935, 1999
123. Stender IM et al: Photodynamic therapy with 5-aminolaevulinic acid or placebo for recalcitrant foot and hand warts: randomized double-blind trial. *Lancet* 355:963, 2000

CHAPTER 267

Lasers in Dermatology

Graeme M. Lipper
R. Rox Anderson

Lasers in medicine defy simple characterization. New technology and new surgical and diagnostic applications for lasers are steadily being conceived. Lasers serve goals as diverse as revascularization of ischemic cardiac tissue, precise sculpting of the cornea, pulverizing urinary stones, and imaging cancers in vivo. Dermatology has been deeply affected by lasers, using them as precise and tissue-selective surgical tools.

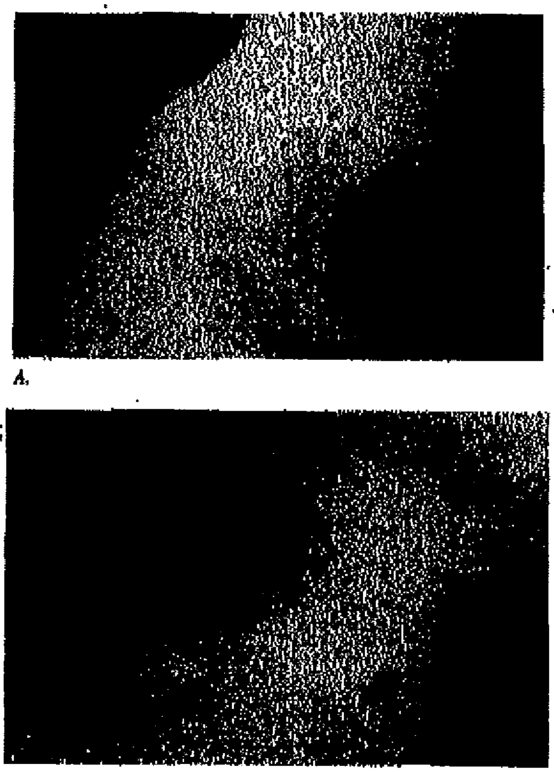
ELECTROMAGNETIC RADIATION AND THE LASER BEAM

For centuries, physicists debated the nature of light. While Maxwell and his English colleagues argued that visible light behaved as particles, Fresnel and the French physicists maintained that light behaved as a wave, accounting for phenomena such as diffraction, constructive and destructive interference. Both views are correct, a "duality" now pervasive in quantum physics. Proof that electromagnetic radiation (EMR) travels as discrete particles, or *quanta,* of energy came when Einstein demonstrated that light can liberate single electrons off of a metal foil plate. This led to the present view that all matter and energy—everything in the universe—is quantized. EMR is now conceptualized as a fundamental form of energy, propagating through space at a constant speed c, as a wave but comprised of discrete quanta known as photons. As expressed by Planck's law ($E = h\nu = hc/\lambda$, where E = energy, ν = frequency, λ = wavelength, c = speed of light, and h = Planck's constant), photon energy is proportional to wave frequency and inversely related to wavelength. Consequently, shorter wavelength photons carry more energy. The EMR spectrum ranges from long-wavelength, low-energy radiowaves and microwaves to short-wavelength, high energy x-rays.

When EMR encounters skin, photons are absorbed by individual molecules, called *chromophores,* and/or scattered by structures in the skin. Scattering is a change in the direction of propagation of light, and accounts for reflection from skin. Absorption extinguishes a photon, and all of the photon energy is transferred to the chromophore molecule that absorbed the photon. Without energy absorption, no photon–tissue interaction can occur. Ionizing forms of EMR such as x-rays and short-wave ultraviolet (UV) light impart enough energy to strip electrons from the absorbing molecules entirely. In contrast, optical radiation has the right quantum energy for moving electrons between their molecular orbit levels. This is the basis for photochemistry, in which a photon provides the activation energy for chemical reactions. For example, visible light is visible because its photon energy exactly matches the activation energy for rhodopsin to isomerize, initiating a retinal action potential. Optical wavelengths are generally expressed in nanometers (1 nm = 10^{-9}m). Infrared radiation, which has a longer wavelength and lower photon energy than visible light, generally excites vibrational and rotational motions, generating kinetic energy (heat).

LASER is an acronym for light amplified by stimulated emission of radiation—a process that explains how the unique characteristics of laser light are obtained, illustrated in Fig. 267-1(*A*). The creation of light is conceptually the inverse of absorption—a photon is created when an electron jumps to a lower-energy orbital. In most light sources, this is a spontaneous, random process. In contrast, laser photons are stimulated into existence by each other. Electrons in the laser medium are first excited to a metastable state, which will eventually return to the preferred ground state by emitting energy. In stimulated emission, a photon triggers the release of metastable state energy in the form of a second, identical photon. Thus, amplification of light is achieved. The

FIGURE 267-5



A. B.

Epidermal nevus in the neck before (A) and after (B) treatment with a rapidly scanned CO_2 laser.

Melasma should be responsive to Q-switched lasers capable of selectively targeting melanin, yet this has not been the case in practice. Rather, all forms of melasma have proven refractory to laser treatment, with recurrence or even pigment darkening being the rule. There is little doubt that Q-switched laser treatment destroys the dermal melanophages present in the dermal form of melasma, but treatment necessarily damages the epidermis in the process, potentiating further melasma. Patients with refractory facial melasma or postinflammatory hyperpigmentation typically do not improve after Q-switched ruby laser treatment.[44] Transient improvement had been noted after using erbium:YAG skin resurfacing to treat refractory facial melasma; however, all patients experienced significant postinflammatory hyperpigmentation.[45] At present, laser treatment of melasma cannot be advocated as a single-line therapy, although judicious use of Q-switched laser irradiation or erbium:YAG resurfacing in combination with topical bleaching creams and sun protection may yield cosmetic improvement in some individuals.

Laser treatment of postinflammatory hyperpigmentation is less disappointing, but variable, especially in darker skin types prone to laser-induced pigment alteration. In lighter skin types, however, Q-switched lasers such as the ruby, alexandrite, and Nd:YAG have been used to treat postsclerotherapy, or drug-induced, hyperpigmentation with good results. In contrast to postinflammatory hyperpigmentation, which is caused by melanin pigment incontinence, postsclerotherapy hyperpigmentation is caused by vessel rupture, erythrocyte extravasation, and perivascular hemosiderin deposition. Tafazzoli et al. used the Q-switched ruby laser (5.6 to 10.5 J/cm^2; 4-mm spot size) to treat this common sclerotherapy complication in eight patients, noting significant lightening in 92 percent of treated areas.[46]

Drug-induced hyperpigmentation may be caused by dermal and epidermal deposition of drug metabolites, hemosiderin, melanin, or a combination of pigment types. The unwanted pigmentation—which can vary from slate-gray to blue, lilac, brown, yellow, or red depending on the culprit drug—often follows a photodistribution (e.g., amiodarone, imipramine), but may also occur on mucosal surfaces, nails, teeth, or in a generalized distribution (e.g., minocycline, busulfan). Q-switched ruby, alexandrite, and 1064 nm-Nd:YAG lasers have all been used to lighten minocycline-induced cutaneous hyperpigmentation with good results. Significant cosmetic improvement has also been reported by using Q-switched lasers to treat amiodarone- and imipramine-induced hyperpigmentation.

Exogenous Dermal Pigment: Tattoos

Prior to the advent of Q-switched laser technology, individuals desiring tattoo removal had to choose between keeping their tattoo or accepting a scar in its place. While a major step forward, Q-switched laser treatment of tattoos is still far from ideal. In skilled hands, ablative techniques, including salabrasion, dermabrasion, cryotherapy, excision, and CO_2 laser vaporization, are capable of yielding cosmetically acceptable results, yet none can promise uniform, scar-free tattoo removal. With the introduction[47] and subsequent refinement of Q-switched laser technology for the treatment of tattoos, selective removal of tattoo pigment without scarring became a real clinical possibility.

An ideal treatment should remove all traces of tattoo pigment without leaving residual scarring. Most tattoo pigment particles are localized to lysosomes, primarily within dermal fibroblasts, macrophages, and occasional mast cells.[48] Pigment particle size ranges from about 2 to 400 nm, with the predominant pigment type being an oval-shaped 40-nm granule. Q-switched lasers produce nanosecond pulses, thereby achieving thermal confinement within individual lysosomes. With Q-switched laser treatment, the irradiated pigment particles reach peak temperatures in excess of 300°C (572°F) within nanoseconds, producing internal changes such as mechanical rupture and chemical alteration (e.g., combustion for carbon-based particles). Taylor et al. and others have described the morphologic appearance of such irradiated pigment particles as "lamellated" or "shell-like," with central zones of lucency and diminished opacity.[45] These intrinsic structural and chemical changes alone may account for some of the tattoo lightening that follows Q-switched laser irradiation. Each heated pigment particle also vaporizes a shell of water surrounding it, creating a shock wave and cavitation that may contribute to the mechanical rupture and dispersion of the pigment throughout the host cell. Cell rupture and release of pigment fragments into the extracellular space occurs, and the ink is partially eliminated via lymphatic drainage, rephagocytosis, or transepidermal elimination—all proposed mechanisms of posttreatment tattoo clearance. Strategies to augment these "pigment-elimination pathways" may hasten the process of tattoo lightening. In addition, there is some evidence that a new generation of picosecond-pulsed lasers may be even more effective at achieving both thermal and inertial confinement within individual tattoo pigment particles, leading to enhanced photoacoustic effects and more effective tattoo pigment clearance.[49] At present, technological and cost constraints have limited the clinical availability of picosecond lasers.

Over the past decade, the term "laser tattoo removal" has found its way into popular culture, and there is a current misconception that modern lasers can simply erase any tattoo. Recently, the incidence of